A slippery disease: a microbiologist's view

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The brachial plexus has always been a mystery to me. As a medical student in 1957, I missed out that part of the course because I was in bed with Asian flu. Memories of its onset are still vivid because the symptoms came on so rapidly and with such strength. We had dipped out of the dissecting room at St Thomas's for a mid-morning break and strolled along the Embankment to Lambeth Bridge. Going there I felt fine. Coming back was terrible because of fever and aching limbs. But the full importance of influenza in 1957 had passed me by—how a new virus (H2N2) had appeared in February in China in Guizhou province, spread to Yunan in March, Singapore and Hong Kong in April, Japan in May, and the United Kingdom in June and July, with a first peak incidence of disease here in October and a second in January 1958. And I did not know then that I had been a victim of the second biggest influenza pandemic in the 20th century.

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Current vaccines are poor immunogens

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Vaccine history

Ronald Hare, professor of bacteriology at St Thomas's, became my boss in 1963. Hare, with others, discovered haemagglutination and developed an egg grown vaccine against influenza. He was working in North America at the time and a major incentive was the US entry into the second world war. The 1918-9 epidemic had killed more American soldiers than the Germans in the first world war.[1] But Hare remained cynical about influenza vaccines. At best they only protected some of the recipients for some of the time. They were poorly immunogenic. And the first to be given on a big scale failed to protect in 1947 because of the big antigenic drift that had happened since 1943, when the seed virus had been isolated.[2]

In the 60 years since much research has been done. Influenza vaccines have improved. But these problems have not been solved: H5N1 vaccines have been made for human use, but they are poor immunogens and there is a reluctance to scale up their production because by the time they are needed—if they ever are—antigenic drift may have substantially reduced their protective power.[3]

When Hare retired in the mid-1960s he was succeeded by Tony Waterson, a virologist and electron microscopist. I was put to work using the techniques and approaches of molecular biology to dissect virus virulence using bird flu (fowl plague virus as it was called then) and its relatives as model systems. Our hope was that characterising the proteins and genes of the virus would explain everything. It was naive. Forty years on, we have a superabundance of sequence information but we still cannot predict with confidence the nastiness of a virus strain or its ability to spread in humans from structural data alone.

New strains

Events in 1976 were grave reminders of outstanding questions about influenza. I was working in Glasgow and attended an autopsy on 24 February on a 20 year old shop assistant who had had a sudden flu-like illness that progressed in under 24 hours to coma, respiratory failure, and death. Her lungs were extensively congested and haemorrhagic and influenza virus was isolated from them. On 4 February, an 18 year old US army recruit at Fort Dix, New Jersey, died after a short acute respiratory illness. Influenza virus was isolated. The Glasgow girl's illness was just like those reported in 1918 and 1919 but she had been infected with an H3N2 virus. It had been circulating since 1968 and was not considered to be unusually virulent. Why had it killed a previously healthy young person?

In New Jersey the situation was different. The virus was H1N1 swine. This was thought to be the 1918-9 subtype that had been so lethal among young soldiers.[4] Perhaps the virus had returned; maybe a pandemic was on the way. Work started on a vaccine on 17 February. In March, President Ford met with experts at the White House and announced a $135m programme to vaccinate "every man, woman and child in the United States."[4] It started in October but was suspended in December after 40 million vaccinations because of a small number of cases of Guillain-Bárre syndrome after vaccination. And the New Jersey swine flu had never spread beyond Fort Dix. After infecting about 230 soldiers it had died out in early February.

Keeping up the chase

At the time, many deemed the 1976 swine flu episode to be a fiasco. But its severest critics entitled their report, *The Swine Flu Affair: Decision-Making on a Slippery Disease*.[4] The virus is slippery because it evolves fast (and evolution is by definition unpredictable) and because of its relation with birds. They can spread it on the wing; and our affection for them either for food or as feathered friends increases their numbers and prevents us from controlling them like mosquitoes or rats. Eradicating the virus cannot even be a pipe dream. A slippery disease would be expected to spring

surprises; when I worked on fowl plague we never contemplated that the virus could infect humans. Lethality never crossed our minds. Our main concern with the large amounts of virus that we slopped around the lab was not to get it on our clothes.

In the past 150 years rich countries have successfully controlled, and sometimes eliminated, infections: cholera and typhoid by clean water, tuberculosis by better diets and milk pasteurisation, and diphtheria, polio, measles, and rubella by immunisation. But for influenza, all countries in the world, rich or poor, remain equally at risk. Whether H5N1 becomes pandemic, or eventually enters the encyclopedia as another Fort Dix false alarm, no one can say. The only certainty is that there will be a flu pandemic, some time. The lesson from history is that making predictions about the virus is a fool's game. It will go on evolving whatever we do. But my guess is that the best way forward is to focus on vaccines: to improve their immunogenicity, their breadth of protection, and the speed of manufacture.

Contributors and sources: THP worked for 15 years on viruses including influenza and smallpox before becoming a bacteriologist, developing a particular interest in using molecular biology to type pathogens such as *Staphylococcus aureus* and *Escherichia coli* 0157. He is currently chairing the public inquiry into the 2005 *E coli* outbreak in south Wales.

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Hard decisions will have to be made: view from intensive care

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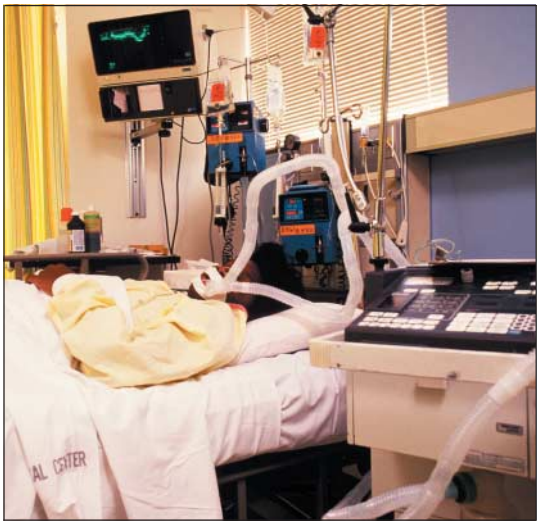
Human mortality from the H5N1 strain of influenza has been high even when antiviral drugs have been used. In most cases death has been due to respiratory failure leading to multisystem failure.[1] These conditions can be managed by mechanical ventilation and organ system support in intensive care units. Such treatments were not generally available during the previous influenza pandemics in 1918, 1957, and 1968, and they will hopefully reduce the excess mortality if the H5N1 strain produces a pandemic. This will be possible only if the limited critical care resources in the UK are used effectively.

Disappointingly, the Health Protection Agency's pandemic plan for influenza does not mention intensive care,[2] although the Department of Health has established a critical care contingency planning group. Critical care networks have also been asked to assess the scope for increasing critical care capacity in an emergency.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Who should get care?

Demand for intensive care

We can estimate the extra demand for intensive care from predictions of the likely extent of the epidemic. The Health Protection Agency model assumes a mortality of 0.37% and a relatively low hospital admission rate of 0.55%, which suggests that only severely ill patients would be admitted to hospital and that a high proportion of these would potentially benefit from intensive care.[2] Of patients with influenza A (H5N1) admitted to hospital in Asia, between 44% and 100% have developed respiratory failure.[1] If pandemic influenza behaves similarly, a large district hospital serving a population of 330 000 could expect more than 10 extra requests for intensive care a day for several weeks at the peak of the epidemic.

The number of critical care beds needed to meet this demand would depend on the duration of care required. In my hospital, patients with pneumonia have a median length of stay on intensive care of five days (unpublished data). If we assume that the flu patients would require a similar duration of mechanical ventilation and organ system support, more than 30 additional intensive care beds would be required to meet this demand. This is between four and five times the number of intensive care beds available in most general hospitals in the UK.

We are unlikely to be able to mobilise the equipment and staff to achieve such a temporary increase in the provision of intensive care. During an epidemic, elective surgery will be reduced to accommodate extra emergency admissions. Ventilators and other equipment from operating theatres and recovery areas could therefore be pressed into service, but staff-